REMARKS

I. The Outstanding Rejections

In the Action, the examiner rejected claims 41-42 under 35 USC §101 as assertedly being drawn to non-statutory subject matter. The examiner further rejected claims 39 and 41 under 35 U.S.C. §102(b) as being anticipated by Martins et al (*J Biol. Chem.* 257:1973-79, 1982) (hereinafter "Martins"), claims 40 and 42 under 35 U.S.C. §102(b) as being anticipated by Murashima et al. (*Biochemistry* 29:5285-92, 1990) (hereinafter "Murashima"), and claims 39 and 41 and claims 40 and 42 under 35 U.S.C. §§102(a) and 102(b), respectively, as being anticipated by Manganiello et al (p. 61-85 in Beavo and Housley, Eds., "Isoenzymes of cyclic nucleotide phosphodiesterases," John Wiley and Sons, 1990) (hereinafter "Manganiello").

Applicants respectfully request reconsideration of the rejections in light of the remarks set forth herein.

II. Objections to the Specification

The examiner objected that the heading "Brief Description of the Drawing" is not included in the specification. The specification has been amended at page 14 to include this heading.

The examiner also objected to the specification as lacking sequence identifiers for all polynucleotide or polypeptide sequences listed in the specification. The application has been amended at page 14, line 4 to insert sequence identifiers for the polypeptide sequences set out in Figure 1.

II. Patentability

A. The Rejection of Claims 41-42 Under 35 U.S.C. §101(a) May Properly Be Withdrawn

The examiner rejected claims 41-42 as being directed to non-statutory subject matter. Claims 41-42 have been amended to recite "An isolated and purified polypeptide product of the expression...," as suggested by the examiner, thereby obviating the rejection.

B. The Rejection of Claims 39 and 41 Under 35 U.S.C. §102(b), as anticipated by Martins, May Properly Be Withdrawn

The examiner rejected claims 39 and 41 as being anticipated under 35 U.S.C. §102(b) by Martins. The examiner contends that Martins discloses isolation of a bovine adrenal cortex cGS-PDE, and that this protein, having a molecular weight of approximately 105-107 kD, must inherently be the protein identified in SEQ ID NO: 39, having a molecular weight of approximately 103 kD.

The specification describes a key element of phosphodiesterase biology that was known in the art when the application was filed, namely that each class of phosphodiesterase (PDE) actually includes several different isoforms, typically having a distinct protein sequence, molecular weight and physiochemical properties. For example, isolation of calcium/calmodulin-specific PDEs (CaM-PDE) from bovine brain revealed two isoforms of approximately 61 and 63 kD (page 9, lines 27-33). These two isoforms, isolated using the exact same isolation method, are only 2 kD different in weight yet are different proteins, i.e., have different amino acid sequences.

The protein described by Martins was isolated through chemical protein purification methods and was not identified by sequence, but only by its molecular weight of approximately 105-107 kD. The protein identified in SEQ ID NO: 39 was identified through recombinant cDNA cloning methods. This protein is identified as having a molecular weight of 103 kD. The

PDE of SEQ ID NO: 39 and that of Martins appear to be at least 2 kD different in molecular weight, which may indicate that these two proteins are different isoforms of each other.

A worker of ordinary skill in the art, reading Martins, would not have reasonably expected the sequence of the Martins PDE protein and the PDE of SEQ ID NO: 39 to be exactly the same. A person of ordinary skill at the time the invention was made would have recognized that PDEs can exist in many different isoforms differing only slightly from each other in molecular weights and sequences. Accordingly, the skilled artisan would have understood that it would be improper to simply assume that a protein identified as having a MW of 105-107 kD was the same protein as that having a MW of 103 kD; more information would be required before such a conclusion could be reached.

Because there could have been no reasonable expectation that the protein of Martins, having a MW of 105-107 kD, would be the exact cGS-PDE isoform set out in SEQ ID NO: 39, having a MW of 103 kD, Martins does not anticipate the present invention and the rejection of claims 39 and 41 under 35 U.S.C. §102(b) should properly be withdrawn.

C. The Rejection of Claims 40 and 42 Under 35 U.S.C. §102(b), as anticipated by Murashima, Should Properly Be Withdrawn

The examiner rejected claims 40 and 42 as being anticipated under 35 U.S.C. §102(b) by Murashima. The examiner contends that Murashima discloses isolation of a bovine brain cGS-PDE, and that this protein, having a molecular weight "slightly greater than from adrenals," (See Action, page 5) must inherently be the protein identified in SEQ ID NO: 43, which was isolated from bovine brain tissue.

Murashima describes chemical isolation of a cGS-PDE from bovine brain and, like Martins, does not provide any sequence information for this protein. The protein identified in SEQ ID NO: 43 was identified through recombinant cDNA cloning methods. In the specification, SEQ ID NO: 43 is compared to the adrenal cortex PDE of SEQ ID NO: 39 (921 aa and a predicted molecular weight of 103 kD), and described as having 20 more amino acid residues than SEQ ID NO: 39 (page 40, lines 12-14).

Murashima evaluates its brain-derived PDE by comparison to a previously identified cGS-PDE from **calf liver**, not from adrenal glands as asserted by the examiner. The sentence bridging pages 5288 and 5289 teaches that the "enzyme from bovine brain cerebral cortex exhibited an M_r slightly greater than that of the cGMP-stimulated PDE purified from calf liver." Calf liver and adrenal cortex are by no means the same tissue source, and it was well-recognized at the time the invention was made that different tissues can express different PDE isoforms (See, e.g., Manganiello, the sentence bridging pages 64-65, which indicates that cGMP-stimulated PDEs had been isolated from bovine cardiac tissue, bovine adrenal tissue and calf liver.) Because a calf liver PDE and an adrenal cortex PDE could be of slightly different sizes, similar to the 2 kD difference in CaM –PDEs noted above, one cannot assume that a calf liver enzyme and an adrenal cortex enzyme are the same enzyme. As such, the examiner cannot properly assert that the Murashima brain-derived PDE is larger than an adrenal PDE. And therefore cannot equate the Mursashima PDE and the PDE set out in SEQ ID NO: 43. Moreover, a worker of ordinary skill in the art cannot reasonably expect that the Murashima PDE and the protein in SEQ ID NO: 43 are the same enzyme based on speculation of molecular weights of PDE isoforms from different tissue sources.

Additionally, similar to the argument presented in Section B above, a worker of ordinary skill in the art, reading Murashima, would not have reasonably expected the sequence of the Murashima PDE protein and the PDE of SEQ ID NO: 43 to be exactly the same. A person of ordinary skill at the time the invention was made would have recognized that PDEs can exist in many different isoforms, some of which exhibit only minor differences in properties, and so would have understood that the Murashima protein could not be assumed to be inherently the same protein as SEQ ID NO: 43 identified herein. Accordingly, the skilled artisan would have understood that it would be improper to simply assume that a protein identified as having a MW slightly greater than a liver PDE (i.e, the PDE described in Murashima) was the same protein as a PDE identified as having more amino acid residues than an adrenal PDE (i.e., the protein set out in SEQ ID NO: 43); more information would be required before such a conclusion could be reached.

Because there could have been no reasonable expectation that the protein of Murashima would be the exact isoform of cGS-PDE set out in SEQ ID NO: 43, one cannot reasonably assert that the protein of Murashima inherently possesses the same sequence as the protein in SEQ ID NO: 43. Therefore, Murashima does not anticipate the presently claimed invention and the rejection of claims 40 and 42 under 35 U.S.C. §102(b) should properly be withdrawn.

D. The Rejection of Claims 39 -42 as Anticipated by Manganiello, Should Properly Be Withdrawn

Based on the asserted priority date of the sequences in SEQ ID NO: 39 and SEQ ID NO: 43, the examiner has rejected claims 39 and 41 under 35 U.S.C. §102(a) as anticipated by Manganiello, and claims 40 and 42 under 35 U.S.C. §102(b) as anticipated by Manganiello. Both rejections will be addressed below.

The examiner contends that Manganiello discloses isolation of, and kinetic properties of, cGMP-simulated PDE isolated from bovine brain and adrenal cortex, and that based on the properties of the PDEs described in Manganiello, these proteins are inherently equivalent to the PDEs set forth in SEQ ID NO: 39 and in SEQ ID NO: 43.

The comparison of the proteins referred to by the examiner, at pages 65-66 and Figure 3.1 of Manganiello, describes the properties of bovine brain cGS-PDE and calf liver PDE, not bovine adrenal and bovine brain PDEs as asserted by the examiner. Assuming that an enzyme isolated from the adrenal gland is the same as an enzyme isolated from the liver is an improper conclusion, especially given the variation in the PDE family of enzymes in the many different organs in which they are expressed. For example, bovine cardiac, liver, brain and adrenal cGS-PDE enzymes have different sequences and kinetic properties (see Manganiello, Table 3.1 and page 66, suggesting that bovine brain and liver PDE have different sequences), and specific functions within their respective organs (see Manganiello, pages 81-82). Thus, one cannot assume that a PDE isolated from the liver is necessarily the same as an adrenal PDE based on their respective molecular weights.

The improper comparison of the calf liver PDE of Manganiello and the adrenal PDE set out in SEQ ID NO: 39 nullifies the examiner's assertion that the PDE proteins disclosed in Manganiello, identified only by molecular weight, must inherently be the same proteins set out in SEQ ID NO: 39 and SEQ ID NO: 43 identified herein. The examiner's argument is based on the assertion that the brain-derived PDE of Manganiello is the same as that set out in SEQ ID NO: 43, and that both these proteins have a molecular weight greater than that of an adrenal PDE, and therefore, the adrenal PDE set out in SEQ ID NO: 39 must be the same as that set out in Manganiello. As stated above, because Manganiello does not even disclose the molecular

weight of an adrenal PDE, the examiner is drawing an improper inference from the Manganiello disclosure, and as such, the disclosure in Manganiello cannot anticipate the proteins set out in SEQ ID NO: 39 and 43.

Because there would have been no reasonable expectation that the proteins disclosed in Manganiello would be the exact isoforms of cGS-PDE set out in SEQ ID NO: 39 or SEQ ID NO: 43, a worker of ordinary skill in the art cannot reasonably predict that the proteins described in Manganiello inherently possess the same sequence as the proteins set out in SEQ ID NOs: 39 and 43. As such, Manganiello does not anticipate the present invention, and the rejection of claims 39 and 41 and claims 40 and 42 under 35 U.S.C. §§102(a) and 102(b), respectively, should properly be withdrawn.

III. Conclusion

Submitted herewith is a check in the amount of $120 pursuant to 37 CFR 1.17 covering a one-month extension of time. If any additional fees are necessary, the Commissioner is authorized to deduct any such fees from Marshall, Gerstein and Borun LLP account 13-2855.

Applicants submit that the application is now in condition for allowance and respectfully request notice of the same.

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Respectfully submitted,

By _____

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